REMARKS

The Official Action dated November 18, 2002 has been carefully considered. Accordingly, the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 12 and 18 are amended for matters of form and clarity in response to the rejection under 35 U.S.C. §112, second paragraph, set forth in the Official Action. A Version With Markings Showing Changes Made is attached. It is believed that these changes do not involve any introduction of new matter and do not raise any new issues subsequent to final rejection, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 12 and 18 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In claim 12 at line 3, the Examiner questioned the meaning of the series of dots. In claim 18, section (e), the Examiner questioned the meaning of "adapted". This rejection is traversed and reconsideration is respectfully requested. In claim 12, the series of dots has been omitted so that claim 12 refers to at least one reactant other than Reactant* as pre-deposited in an application zone LZ_nR for liquid intended for transport of the reactant. Additionally, claim 18, section (e) has been amended to more clearly recite that the device is adapted to transport the $liquid_{n+1}$ through the matrix immediately after $liquid_n$ added to the nearest downstream application zone LZ_n. It is therefore submitted that the claims as amended are definite and that the rejection under 35 U.S.C. §112, second paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 1-4, 6-14, 18-28, 32 and 33 were rejected under 35 U.S.C. §102(b) as being anticipated by the Dafforn et al U.S. Patent No. 4,981,786. The Examiner asserted that Dafforn et al disclose an immunoassay device and method employing a first means for

introducing a sample into the device and a second means for introducing a liquid reagent other than the sample into the device upstream of the sample, with both application zones located upstream of an immunosorbing detection zone. The Examiner further asserted that Dafforn et al disclose specific binding members immobilized in the immunosorbing zone and that the application of liquid can be performed simultaneously in the application zones.

Claims 15, 16, 29 and 30 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Robinson et al published PCT application WO 95/16914. The Examiner relied on Robinson et al as disclosing the use of calibration zones. The Examiner asserted it would have been obvious to incorporate the use of a calibrator zone as taught by Robinson et al in the method and device of Dafforn et al.

Finally, claims 17 and 31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Dafforn et al in view of the Self U.S. Patent No. 4,446,231. The Examiner relied on Self as disclosing that immunoassays are used for the detection and/or determination of autoimmune diseases. The Examiner asserted it would have been obvious to use immunoassays as taught by Self for the diagnosis of autoimmune diseases.

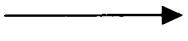
In response to the arguments set forth in Applicants' previous Amendment, the Examiner asserted that Dafforn et al disclose that the application of liquid reagent and sample can be sequential or simultaneous. The Examiner further asserted that one skilled in the art would recognize that if the liquid reagent and sample are applied simultaneously, they would both contact the flow matrix almost simultaneously and since the sample is located downstream from the liquid reagent, the liquid reagent would be transported through the matrix immediately after the sample.

However, Applicants submit that the methods, devices and test kits defined by claims 1-4, 6-14 and 18-28 are not anticipated by nor rendered obvius over Dafforn et al, alone or in

combination with Robinson et al or Self. Accordingly, these rejections are traversed and reconsideration is respectfully requested.

More particularly, as defined by claims 1 and 18, the present invention is directed to methods and devices for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I). The flow matrix comprises an application zone for liquid (LZ) containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I, a detection zone with Reactant I located downstream of LZ, and optionally one or more zones in which any of the reactants has been pre-deposited. The flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other :

$LZ_m \ldots LZ_n \ldots LZ_l$ DZ

flow direction 

wherein LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n, m is the total number of application zones in which flow is initiated ($m \geq 2$), one LZ_n is an application zone for sample (LZ_n'S) and one LZ_n is for Reactant* (LZ_n"R*), with $n'' \geq n'$, ⟶ is the direction of the flow, and DZ is the detection zone. Flow is initiated by adding liquid to each zone $LZ_m \ldots LZ_n \ldots LZ_l$ ($m \neq n$) in such a way that $liquid_{n+1}$, added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$ added to the nearest downstream application zone LZ_n. The present methods and devices facilitate automation of analyte determination, avoid the need for sequential addition of sample and analytically detectable reactant, and allow for predeposited analytical reactant for sequential methodologies.

Daffom et al disclose a multiple port assay device. Delivery of a sample may be made into the device through a first means or second means using a dropper, syringe needle, etc., resulting in deposit of the sample on a bibulous strip, and a liquid reagent other than sample may be added to the device. Additional liquid reagents may be added to the device either before or after sample addition, at least one of such reagents being added through the means not used for adding the sample (column 13, lines 32-42). The application of reagents can also be done by breaking the container (column 23, line 52).

However, Applicants find no teaching or suggestion by Daffom et al relating to a method or device as presently claimed wherein at least one biospecific affinity reactant (Reactant I) is firmly anchored in the flow matrix and at least one biospecific affinity reactant is applied to an application zone in combination with a flow matrix arrangement as recited in claims 1 and 18. Particularly, Applicants find no teaching or suggestion by Daffom et al of a method or device wherein flow is initiated by adding liquid to each zone in such a way that $liquid_{n+1}$ added to the application zone LZ_{n+1} contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n.

In fact, the only specific mention of simultaneous application which Applicants find in the teachings of Daffom et al is at column 24, beginning at line 22 wherein an assay is described as conducted by adding a sample suspected of containing human chorionic gonadotrophin (HCG) at a first opening and simultaneously adding a developer solution containing enzyme substrate at the second opening. However, contrary to the present methods and device wherein $liquid_{n+1}$ added to the application zone LZ_{n+1} contacts the flow matrix substantially simultaneously and is transported through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n, Daffom et al disclose that the sample HCG binds to an enzyme conjugate and the resulting complex is carried by the

moving developer solution to the detection zone where it binds. Thus, Applicants find no teaching or suggestion by Daffom et al that liquid reagent added simultaneously with a sample is transported through a matrix immediately after the sample. Rather, Daffom et al teach that HCG-conjugate complex is carried by the moving developer solution to the detection zone. Daffom et al provide no teaching or suggestion relating to simultaneous application with a sequential flow of reagents through a matrix.

Thus, in the present methods and devices, sample and reagent may be applied to the flow matrix simultaneously. The sample begins migration to the detection zone and is followed by liquid migration from the next upstream zone. As a result, there is a continuous migration of sample and reagents through the flow matrix, started by one initial application occasion. The flow of liquids through the flow matrix and the detection zone is in the same order as they are added in the application zone. Applicants find no such teachings by Daffom et al.

Anticipation under 35 U.S.C. §102 requires that each and every element set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 49 U.S.P.Q.2d 1949, 1950 (Fed Cir. 1999). In view of the deficiencies in the teachings of Daffom et al with respect to simultaneous application and sequential transport, Daffom et al do not anticipate the present claims under 35 U.S.C. §102. It is therefore submitted that the rejection under 35 U.S.C. §102 based on Daffom et al has been overcome. Reconsideration is respectfully requested.

Moreover, the deficiencies of Daffom et al are not resolved by Robinson et al or Self. Robinson et al describe a sensor device for a sandwich assay comprising a discrete zone having a measurement region on which is immobilized a first specific binding partner for a ligand under assay and a known amount of a releasable optionally labeled second specific binding partner for the ligand under assay, and a second discrete zone having a region on

which is immobilized a first specific binding partner for the ligand under assay, a releasable known amount of ligand analog, and a second known amount of a second optionally labeled second specific binding partner for the ligand under assay.

However, Applicants find no teaching or suggestion for employing any of the elements of Robinson et al's sensor device in the multiple port assay device of Dafforn et al. In fact, while Dafforn et al require application of one or more liquid reagents in addition to a liquid sample through different introduction means, the sensor device of Robinson et al is designed for a sandwich assay wherein only a sample containing a ligand under assay is applied. Additionally, Applicants find no teaching or suggestion by Robinson et al of a method or device as recited in claims 1 and 18, respectively, employing at least one analytically detectable biospecific affinity reactant (Reactant*) and at least one firmly anchored biospecific affinity reactant (Reactant I) in a detection zone, with the arrangement of liquid application zones and liquid flows as recited in claims 1 and 18.

In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). In view of the failure of Robinson et al to resolve the deficiencies of Dafforn et al, particularly with respect to a method and device allowing simultaneous application and sequential transport, the combination of these references does not enable one of ordinary skill in the art to conduct the claimed method or make and use the claimed device. Thus, the combination of Dafforn et al and Robinson et al does not render the present claims obvious.

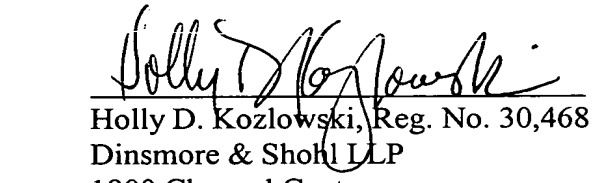
Finally, while Self discloses an immunoassay using an amplified cyclic detection system, Applicants find no teaching or suggestion by Self relating to a method or device for determination of an analyte in a sample and a flow matrix employing a combination of biospecific affinity reactants and liquid application zones and flow as defined in claims 1 and

18. Similarly, Applicants find no teaching or suggestion by Self for modifying any of the teachings of Daffom et al to result in either a method or a device as presently claimed. Thus, the mere teaching by Self of the use of immunoassays for detection and/or determination of autoimmune diseases does not resolve the deficiencies of Daffom et al, particularly with respect to a method and device allowing simultaneous application and sequential transport. Thus, the combination of Daffom et al and Self does not render the methods and devices of the present claims obvious.

It is therefore submitted that the rejections of the claims under 35 U.S.C. §103 based on Daffom et al and Robinson et al or Self have been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102, 103 and 112, second paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested. In the event that the present Amendment does not place the present application in condition for allowance, entry of the present Amendment for purposes of appeal, specifically placing claims 12 and 18 in better form for appeal, is respectfully requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

In the Claims:

Please amend claims 12 and 18 to read as follows:

12. (Twice Amended) The method according to claim 1, wherein at least one reactant, other than Reactant*, is pre-deposited in an application zone [LZ_n...R] $\underline{LZ_nR}$ for liquid intended for transport of the reactant.

18. (Third Amendment) A device for determination of an analyte in a sample in a flow matrix by use of a transport flow of one or more biospecific affinity reactants, at least one of which is analytically detectable (Reactant*) and one of which is firmly anchored in the matrix (Reactant I), said device comprising a flow matrix having:

A) an application zone for liquid (LZ), containing buffer and sample and optionally reactants needed for a complete determination, but not Reactant I,

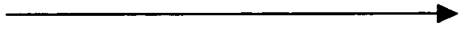
B) a detection zone (DZ) with the firmly anchored reactant (Reactant I) located downstream of LZ, and

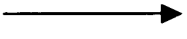
C) optionally one or more zones in which any of the reactants has been pre-deposited,

wherein

the flow matrix comprises at least two application zones for liquid arranged substantially adjacent to each other:

$LZ_m \ldots LZ_n \ldots LZ_l$ DZ



flow direction 

wherein

a) LZ_n is an application zone for liquid, and n is the position of the application zone LZ_n,

b) m is the total number of application zones in which flow is initiated ($m \geq 2$),

c) one LZ_n is an application zone for sample (LZ_n,S) and one LZ_n is for Reactant* ($LZ_{n''}R^*$) with $n'' \geq n'$;

d) ⟶ is the direction of the flow, and

e) DZ is the detection zone, wherein [the device is adapted], when flow is initiated by adding liquid to each zone LZ_m . . LZ_n . . LZ_1 ($m \neq n$) in such a way that $liquid_{n+1}$ added to the application zone LZ_{n+1}, contacts the flow matrix substantially simultaneously, the device is adapted to transport the liquid $_{n+1}$ through the matrix immediately after $liquid_n$, added to the nearest downstream application zone LZ_n.